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DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rabbits

ACCESSION NUMBER: 265389

TOX. CHEM. NO.: 273H

TEST MATERIAL: Technical S-3206
Batch No. 20514

MRID NO.: N/A

00163516

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 181/84667

SPONSOR: Sumitomo Chemical America, Inc. (Sumitomo No. FT-51-0134)

TESTING FACILITY: Huntingdon Research Centre (England)

TITLE OF REPORT: The Effect of S-3206 on Pregnancy of the New Zealand White Rabbit

AUTHOR(S): D.C. Cozens, E.W. Hughes, R.E. Masters, and A. Anderson

REPORT ISSUED: November 13, 1985

CONCLUSIONS: There were no compound-related effects on reproduction, and no dose-related effect on the incidence or types of malformations and anomalies observed. The following are the defined doses for this study:

Maternal NOEL = 4 mg/kg/day
Maternal LEL = 12 mg/kg/day [Grooming, anorexia, flicking of the forepaws]
Fetotoxic NOEL >36 mg/kg/day
Embryotoxic NOEL >36 mg/kg/day
Teratogenic NOEL >36 mg/kg/day
A/D Ratio (Adult/Developmental Ratio = Maternal LEL/Teratogenic LEL) = 12 mg/kg/day/>36 mg/kg/day = <0.33

STUDY CLASSIFICATION: This study is classified CORE GUIDELINE. It received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed in three parts, a pilot study to establish dose levels, a preliminary study, and a teratology study. The test article, S-3206 (92.5% pure), was formulated daily by heating it to 80°C, and then diluting it with corn oil vehicle. The dose volume for all studies was 0.5 ml/kg.

In the Pilot Study, 4 groups of 2 nonpregnant female New Zealand rabbits each (26-31 weeks old) were given seven daily administrations of S-3206 by gastric intubation at doses of 20, 30, 45, and 67.5 mg/kg/day. Dosing began on days 0, 3, 5, and 7, respectively. The rabbits were observed and weighed daily, then sacrificed after 7 days of treatment.

In the Preliminary Study, 5 groups of 6 nonpregnant female New Zealand rabbits each (14-17 weeks old) were given 13 daily administrations of S-3206 by oral gavage at doses of 0 (vehicle control), 15, 22, 33, and 50 mg/kg/day. Dosing began on day 0. Each formulation was analyzed for dose concentration.

The rabbits were observed daily. They were weighed twice pretest, once prior to dose initiation, and daily during the study. Food consumption was measured over the course of the study. All rabbits were sacrificed 8 days after the final dosing, and examined grossly.

In the Teratology Study, 4 groups of nonpregnant female New Zealand rabbits (14-17 weeks old) were mated with males of proven fertility. An hour after coitus, the does were dosed with Chorulon® lutenizing hormone to assure ovulation. The groups initially consisted of 18, 17, 19, and 17 rabbits, respectively. They were given 13 daily administrations of S-3206 by oral gavage on gestation days 7 through 19 at doses of 0 (vehicle control), 4, 12, and 36 mg/kg/day. Each dose formulation was analyzed for dose concentration.

The rabbits were observed daily, and weighed on gestation days 1, 7, 11, 15, 20, 24, and 29. Food consumption was measured between the weighing intervals. The does were sacrificed on day 29 by cervical dislocation and examined grossly. Their ovaries and uteri were examined for corpora lutea, live young, embryonic and fetal deaths, fetal weights, and fetal abnormalities.

The live young were weighed and sexed, then sacrificed with sodium pentobarbitone for visceral examination. Microdissection and histopathologic evaluation were used as needed to better describe a finding. The pups were then skinned, eviscerated, and fixed in 74 OP industrial methylated spirit. The heads were sliced along the frontoparietal suture line, and examined for gross abnormalities. The carcasses were then clarified, stained by a modified Dawson technique, and examined for skeletal defects.

RESULTS:

Pilot Study - Dose-related clinical signs included nasal or eye exudate, anorexia, grooming, flicking of the forepaws, tremors or shaky movement, and unsteadiness. One rabbit each at the 30 and 67.5 mg/kg/day doses had yellow stained perianal fur, and a 45 mg/kg/day rabbit had an enlarged liver with subcapsular pale areas. Body weight gain was not significantly altered. Abscesses were found in some animals, but in the absence of a control group the significance of these lesions is uncertain.

Preliminary Study - Dose-related clinical signs seen in the preliminary study included grooming, anorexia, flicking of the forepaws, scratching and chewing of the cage, tremors and shaky movements, and unsteadiness. Neither body weight gain nor food consumption were significantly altered. The observed gross lesions were probably not compound-related.

Teratology Study - Dose-related clinical signs included grooming, anorexia, flicking of the forepaws, flicking of the hind feet, shaky movements and trembling, stamping of the hind feet, and lethargy. Neither body weight gain nor food consumption were significantly altered. There were no compound-related gross lesions. There was one death and several dams were sacrificed moribund, but no deaths were attributed to treatment. The following tables present the status of the dams and offspring:

Dose (mg/kg/day)	Mated/ Gravid*	Implants Per Dam	Live Young Per Dam	-Embryonic Deaths- Early	Late	Abortions	Implantation Loss Pre %	Post %
0	15/15	9.5	8.5	0.3	0.6	0	17.6	10.2
4	15/13	8.9	7.8	0.7	0.5	0	13.8	13.2
12	15/15	9.3	8.5	0.1	0.6	0	9.7	10.1
36	15/13	9.1	8.5	0.2	0.5	1	15.3	7.7

Dose (mg/kg/day)	Fetuses Examined	Mean Fetal Weight (g)	% Male	Total Malformations	Total Anomalies Visceral	Skeletal
0	128	43.4	56	1	8	19
4	101	44.8	51	1	6	24
12	127	43.5	48	0	4	20
36	110	43.5	57	0	4	21

* Several does were replaced prior to treatment, found dead, sacrificed moribund, or excluded from the study due to congenital abnormality. These values represent the population status as of day 29.

One high-dose dam was not pregnant at day 29, and another dam aborted. These findings are probably not significant since all other data show that there were no compound-related effects on reproduction. There was also no dose-related effect on the incidence or types of malformations and anomalies observed.

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Danitol: Developmental Toxicity Study in Rabbits
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